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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,861	12/05/2007	Adrian Ashley	TEVE-111US	8141

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,861	ASHLEY ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-11 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 12/31/2009 were entered.

Response to Arguments

2. Applicant's arguments, filed 12/31/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. In particular, the rejection of claim 1 under 35 USC 102(b) has been withdrawn in view of Applicant's amendments to the claim. Also, the rejection of claims 2-7 and 9 under 35 USC 102(b) has been withdrawn in view of Applicant's arguments, which are considered persuasive. Applicant's arguments to withdrawn rejections are rendered moot. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 1-2, 4-6, 8-11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Gentile et al* (cited in a previous Action) as applied to claim 2 above, in further view of *Karlsson et al* (cited in a previous Action) and *McAffer et al* (cited in a previous Action).**

6. As amended, instant claim 1 is drawn to a method for the sterilization of a labile glucocorticosteroid (for example, budesonide or beclomethasone dipropionate as recited by instant claims 9-11) comprising the step of applying a moist heat to an aqueous suspension of a labile glucocorticosteroid for a sterilizing-effective time, wherein at least 70% of the glucocorticosteroid is in the form of a suspension during heating and at least one surfactant is present.

7. Support for the above amendments can be found in claims 2 and 7 as originally filed and Paragraph 0030 of the Specification.

8. And, as amended, instant claim 2 is drawn to a method for the sterilization of a glucocorticosteroid (e.g., budesonide or beclomethasone dipropionate as recited by instant claims 9-11) comprising the step of heating (at a temperature of about 101°C to about 145°C as recited by instant claim 4; by autoclaving, as recited by instant claim 5; for about 2 to 180 minutes as recited by instant claim 6; and even more specifically at a temperature of about 121°C for about 20 to 30 minutes as recited by instant claim 10) an aqueous suspension of a glucocorticosteroid, wherein the glucocorticosteroid has a sufficiently low solubility in water and is used in a sufficient amount such that at least 70% of the glucocorticosteroid is in the form of a suspension

during heating (even more specifically at a concentration of from about 15 mg/ml to about 150 mg/ml as recited by instant claim 13), wherein the said suspension comprises a surfactant (more specifically at a concentration of from about 0.75 mg/ml to about 60 mg/ml as recited by instant claim 8).

9. Support for the amendments to claim 2 can be found in claim 7 as originally filed and Paragraph 0030 of the Specification.

10. As discussed in the previous Action mailed on 8/03/2009, *Gentile et al* (EP 1454636) teach a process for the sterilization of a glucocorticoid - which is synonymous with the term glucocorticosteroid as acknowledged by the instant Specification (Paragraph 0021) – and specifically, the glucocorticosteroid **beclomethasone diproprionate** – comprising the step of applying a moist heat to and heating (via autoclave) an aqueous suspension of a glucocorticosteriod and water (Paragraphs 0013-0014) wherein the "glucocorticoid:water ratio is preferably between 3:100 (about 30 mg/ml) to 10:100 (about 100 mg/ml)" (Paragraph 0016) and that "preferably steam sterilization was carried out at 121°C for 20 minutes" (Paragraph 0018). Accordingly, it is asserted that - absent evidence to the contrary - *Gentile et al* teach a process for the sterilization of a glucocorticoid wherein the glucocorticosteriod has a sufficiently low solubility in water and is in a sufficient amount such that at least 70% is in the form of a suspension during heating. As stated in *In re Best, Bolton, and Shaw*, "Where… the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product" 562 F2d 1252 (CCPA 1977). See also *In re Fitzgerald* 619 F2d 67 (CCPA 1980): the burden is

shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on."

11. Although *Gentile et al* do not teach the method comprising ***budesonide*** as recited by instant claims 10 and 13, and as elected by Applicant, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to substitute one known glucocorticosteroid (e.g., beclomethasone diproprionate) with another structurally and functionally similar glucocorticosteroid (butesonide) in the method taught by *Gentile et al* to sterilize said structurally and functionally similar glucocorticosteroid in the same way and with a reasonable expectation of success.

12. As such, *Gentile et al* teach a method for the sterilization of a labile glucocorticosteroid as recited by instant claims 1-2, 4-6, 9-11 and 13 **except that** *Gentile et al* do **not** teach the method wherein at least one surfactant is present in the aqueous suspension during heating as recited by instant claims 1 and 2.

13. Yet, as discussed in the previous Action, the inclusion of surfactants in glucocorticoid suspensions is well known in the art. Specifically, as discussed by *Karlsson et al*, "[t]o obtain an efficient dispersion of the glucocorticosteroid particles in the suspension, a surfactant may be used… The surfactants may also function as stabilizing agents" (Column 5, Lines 21-24). Indeed, *Gentile et al* disclose formulations further comprising a surfactant in the range recited by instant claim 8 (Paragraph 0067, Table 9 and Paragraph 0075, Table 10). Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to include a surfactant as recited by instant claims 1 and 2, at a concentration within the range recited by instant claim 8, to provide stabilizing agents and to obtain an efficient

dispersion of budesonide particles in the suspension with a reasonable expectation of success. Although neither *Karlsson et al* nor *Gentile et al* disclose adding the surfactant to the suspension ***prior to*** sterilization by moist heat as recited by the instant method, it would have been within the purview of the ordinarily skilled artisan to include the surfactant ***before*** heat sterilization in view of *McAffer et al* which disclose methods of sterilizing suspensions comprising budesonide and a surfactant via moist heating (Paragraph 0057). Although *McAffer et al* state that autoclaving the suspension comprising budesonide and a surfactant at 121°C for 15 minutes "resulted in unacceptable increases in the impurity levels present in budesonide suspensions [and thus is not] likely to be acceptable for the sterilization of budesonide" (Paragraph 0067), the skilled artisan would have not considered this a teaching away from the *prima facie* obvious method discussed above since similar methods taught by the prior art also failed to effectively sterilize beclomethasone diproprionate. In particular, *O'Neill* discloses that moist heat sterilization of suspensions comprising glucocorticiods is not suitable for suspensions of fine particles intended for inhalation due to agglomeration and *Bernini et al* disclose that moist heat sterilization of suspensions comprising beclomethasone diproprionate resulted in significant increase in degradation products (Instant Specification, Pages 2-3). Yet, contrary to prior art, the method taught by *Gentile et al* (i.e., moist heat sterilization of suspensions comprising beclomethasone diproprionate at 121°C for 20 minutes) did not provide significant crystal growth or result in degradation (Paragraphs 0052 and 0055) and did effectively sterilize the suspensions comprising beclomethasone diproprionate. Accordingly, the skilled artisan would have expected that the method taught by *Gentile et al* – which overcomes the problems taught by the prior art associated with sterilizing glucocorticosteroids (in particular beclomethasone diproprionate) using moist

heat – would successfully overcome the problems taught by the prior art associated with sterilizing structurally and functionally similar glucocorticosteroids such as budesonide.

14. Accordingly, for all the foregoing reasons, instant claims 1-2, 4-6, 8-11 and 13 are rejected as *prima facie* obvious.

15. Instant claim 14 is drawn to the method of claim 13 further comprising the step of diluting the suspension to a pharmaceutically acceptable concentration. *Gentile et al* specifically disclose preparing final formulations that were mixed and diluted with water (Paragraphs 0071-0075 and Tables 10 and 11) which is asserted to encompass a pharmaceutically acceptable concentration as recited by instant claim 14.

16. As such, instant claim 14 is also rejected as *prima facie* obvious.

17. Applicant traverses on a variety of grounds. First, Applicant argues that the water solubility of different glucocorticosteroids varies depending upon the chemical structure of the particular glucocorticosteroid. And *Gentile et al* teach aqueous suspensions comprising about 30 mg/ml to about 100 mg/ml of glucocorticosteroid regardless of the glucocorticosteroid being sterilized. Yet, the instant invention has discovered that favorable results are obtained when the amount of water relative to the particular glucocorticosteroid being sterilized is selected such that at least 70% of the glucocorticosteroid remains in suspension during heating. As such, Applicant concludes that nothing in *Gentile et al* would have made it obvious to control the proportion of glucocorticosteroid staying in suspension such that it is maintained at a certain minimum level (Applicant Argument, Pages 11-12).

18. In response to Applicant's argument, Applicant is reminded that the USPTO is not equipped with analytical instruments to test prior art compositions for the infinite number of

ways that a subsequent Applicant may present previously unmeasured characteristics. As such, as discussed in the previous Action and reiterated above, it has been asserted that - ***absent evidence to the contrary*** – that *Gentile et al* teach a process for the sterilization of a glucocorticoid wherein the glucocorticosteriod is in a sufficient amount such that at least 70% is in the form of a suspension during heating. Applicant has introduced no evidence to refute this assertion. In fact, as argued by Applicant, "[t]he solubility of budesonide at the sterilization temperature is such that the budesonide concentration must be at least about 23 mg/ml in order for the claim limitation of 'at least 70% of the glucocorticosteroid is in the form of a suspension' to be met" (Applicant Argument, Page 8). Since *Gentile et al* teach aqueous suspensions comprising about 30 mg/ml to about 100 mg/ml of glucocorticosteroid, it is evident that the disclosed suspensions would, in fact, meet the limitation of 'at least 70% of the glucocorticosteroid is in the form of a suspension'. Accordingly, Applicant's argument is not considered persuasive.

19. Applicant's next argue that it would not have been obvious to include a surfactant in the aqueous suspension during heating (Applicant Argument, Page 12). Applicant first argues that *Karlsson et al* is concerned with dry sterilization of powdered forms of glucocorticosteroid (Applicant Argument, Page 12). While this is accurate, the teaching of *Karlsson et al* that "[t]o obtain an efficient dispersion of the glucocorticosteroid particles in the suspension, a surfactant may be used… The surfactants may also function as stabilizing agents" is not so limited. That is, the skilled artisan would not read *Karlsson et al* to motivate the use of surfactants to enhance the dispersion of glucocorticoids in suspension **only** under the limited circumstances discussed therein. Clearly, a person of ordinary skill in the art would recognize the application of the

teaching of *Karlsson et al* to other situations. Next, Applicant argues that *Gentile et al* teach a surfactant may be formulated together with the aqueous glucocorticosteroid suspension after sterilization of the suspension and, given the problems described in paragraphs 0008 to 0010 in *Gentile et al*, the skilled artisan would not have been motivated to include the surfactant prior to sterilization by moist heating (Applicant Argument, Page 12). Yet, as noted in *In re Burhans*, 154 F.2d 690 (CCPA 1946), the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. In the instant case, there is no evidence of new or unexpected results. Furthermore, as discussed in the previous Action and reiterated above, the skilled artisan would have considered including the surfactant ***before*** heat sterilization in view of *McAffer et al* which disclose methods of sterilizing suspensions comprising budesonide and a surfactant via moist heating (Paragraph 0057, Paragraph 0073 and Table 5). As to Applicant's argument that "[t]he teachings of the McAffer reference… fails to disclose a method for sterilizing a labile glucocorticosteroid wherein moist heat is applied to an aqueous suspension of a labile glucocorticosteroid for a sterilizing-effective time, with at least 70% of the glucocorticosteroid being in the form of a suspension during heating and at least one other surfactant being present" (Applicant Argument, Page 13), Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986). Although *McAffer et al* state that autoclaving the suspension comprising budesonide and a surfactant at 121°C for 15 minutes "resulted in unacceptable increases in the impurity levels present in budesonide suspensions [and thus is not] likely to be acceptable for the sterilization of budesonide" (Paragraph 0067), the skilled artisan would have

not considered this a teaching away from the *prima facie* obvious method discussed above since similar methods taught by the prior art ***also*** failed to effectively sterilize beclomethasone diproprionate whereas the method disclosed by *Gentile et al* was successful (see discussion above). As such, it is not considered persuasive that the skilled artisan would not have had a reasonable expectation of success applying the prior art teachings as discussed above. Applicants are reminded that obviousness does not require absolute predictability, only a reasonable expectation of success of obtaining similar properties. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

20. For all the foregoing reasons, Applicant's arguments are not considered persuasive. Claims 1-2, 4-6, 8-11 and 13-14 are rejected as *prima facie* obvious.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

22. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

23. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. **Claims 1-4, 6-7, 9-13 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6, 9-10, 13 and 15 of copending Application No. 11/667,872**.

25. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons: As discussed above, instant claim 1 is drawn to a method for the sterilization of a labile glucocorticosteroid (budesonide or beclomethasone dipropionate as recited by instant claims 9-11) comprising the step of applying a moist heat to a suspension of a labile glucocorticosteroid for a sterilizing-effective time. And instant claim 2 is drawn to a method for the sterilization of a glucocorticosteroid (budesonide or beclomethasone dipropionate as recited by instant claims 9-11) comprising the step of heating (at a temperature of about 101°C to about 145°C as recited by instant claim 4; by autoclaving, as recited by instant claim 5; for about 2 to 180 minutes as recited by instant claim 6; and even more specifically at a temperature

of about 121°C for about 20 to 30 minutes as recited by instant claim 10) an aqueous suspension of a glucocorticosteroid, wherein the glucocorticosteroid has a sufficiently low solubility in water and is used in a sufficient amount such that at least 50% (more specifically, at least 60% as recited by instant claim 3) of the glucocorticosteroid is in the form of a suspension during heating (even more specifically at a concentration of from about 15 mg/ml to about 150 mg/ml as recited by instant claims 12-13), the said suspension further comprising a surfactant as recited by instant claim 7 (at a concentration of from about 0.75 mg/ml to about 60 mg/ml as recited by instant claim 8).

26. The '872 application teaches a method for preparing a sterile suspension of a glucocorticoid comprising heating an aqueous glucocorticoid suspension (more specifically beclomethasone or budesonide as reicted by claims 9-10) at a concentration of from about 15 to about 300 mg/ml (claim 6) and wherein at least 60% is in suspension (claim 8) further comprising a surfactant (claim 3) at a temperature from about 122°C to about 138°C (claim 13) for at least about 30 minutes (claim 15).

27. Although the '872 application does not recite that at least 70% is in suspension as recited by the instant claims, it is asserted that this is necessarily the case.

28. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Padmanabhan "Paddy" Sreenivasan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642